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EXAMINER
PATEL, SUDHAKER B

ART UNIT	PAPER NUMBER
1624	10

DATE MAILED: 06/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,276	ALLEN ET AL.	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *4-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9,11-14,16* is/are rejected.

7)☒ Claim(s) *10 and 15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of invention of Group II, and species disclosed in claim 14 page 183, line 7 in Paper No. 9 dated 5/13/03 is acknowledged. The traversal is on the ground(s) that applicants can claim independent and distinct inventions in a single application. The traversal is on the ground(s) that different structures are not the basis for "special technical features" as per PCT Rules. This is not found persuasive because the inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: They have different chemical structures. The claims lack unity of invention because compounds of Formula (I) do not possess single structural element that is shared by all of the alternatives. The only common technical feature shared by all of the alternatives of the Formula A-B of generic claim 1, namely, 2-Aryl indole-6- C(=NH)-NH2 core, is old. The common structural feature of Formula A - B is not a patentable advance over the prior art(s).

For applicants' quick reference "Unity of Invention rule 37 CFR 1.475" is recited below:

37 CFR 1.475. Unity of invention before the International Searching Authority, the International Preliminary Examining Authority and during the national stage.
(a) An international and a national stage application shall relate to one invention only or to a
group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention "). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features "

shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.
(b) An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:
(1) A product and a process specially adapted for the manufacture of said product; or
(2) A product and a process of use of said product; *or*
(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
(4) A process and an apparatus or means specifically designed for carrying out the said process; or
(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.
(C). If an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b) of this section, unity of invention might not be present.
(d) If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and § 1.476(c).
(e) The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

Examiner has considered (b) (2) and **(C).** of above guidelines as per rule 37 CFR 1.475 for the restriction/election of this application as stated above.

Following different cores are formed for the variables recited in claim:
1). Bicyclic heterocycle when A = Benzimidazole; B = Phenyl;
2). Bicyclic heterocycle when A = Indole; B = Phenyl;
3). Bicyclic heterocycle when A = Pyrido-imidazole; B = phenyl;
When B is other than phenyl i.e.6-membered heterocycle(s) wherein W1, W2, W3, W3 are either C or N, several structures other than simple phenyl are generated which are different chemicals than 2-phenyl-Indole.
The structural combinations are:
Indole- pyridine;
Indole-pyrimidine;
Indole-pyrazine;
Indole –triazine(s).

The claims are drawn to structurally dissimilar compounds, which are classified separately, require separate literature searches and are not art recognized equivalents. They are made and used independently. Each core will require separate search, and

additionally, the utility class will constitute different class which will be time consuming and burdensome to examiner.

Applicants have elected invention of Group II with the species of Example as species disclosed in claim 14 page 183, line 7 (already stated above). Since claims 1-3, 9-19 link with other inventions they will be examined bearing in mind the elected subject matter as per invention of Group II and species as elected by the applicants only. Claims 4-8 are withdrawn from further consideration as they consist of non-elected subject matter. .37 CFR 1.142(b).

Search was carried out with species for the Formula A -B with variables defined as follows:

A	= Partially unsaturated bicyclic heterocycle = indole;
B	= 6-membered unsaturated phenyl;
R1	=OH;
R2	= Aryl = phenyl;
R3, R4, R4	=H;
5-indole position	=-C(=NH)-NH2 ;
R20	= H.

Applicants are reminded of the election of species guidelines provided in MPEP 803.02, which are followed for examination.

The elected species was not found. Therefore, search was expanded to R2 = H in the above defined variables, and an art was found.

As per the guide lines outlined earlier, the search was limited to A = indole; B= phenyl, and the variables:

R1	= OH, halogen, alkyl, S-alkyl;
R2-R5	= H,, Halogen,CN, alkyl,SH, OR10;
R6/R8/R9	= H,Halogen,CN,alkyl,NO2, O-Aryl,O-alkyl;
R7	=-C(=NH)-NH2, CONH2, C(=NH0-NH-NH2.

All other definitions of components A, R7, R1-R6, R8,R9, R20 than stated above are withdrawn from further consideration by the examiner. Additionally, claims 4-8 are also withdrawn from further consideration as they constitute non-elected subject matter. 37 CFR 1..142(b).

Note that compounds, corresponding compositions, a method of use and a process of making that are of the ***same scope*** are considered to form a single inventive concept under PCT Rule 13.1, 37 CFR 1.47(d). The scope that a prior art anticipating one compounds under 35 U.S.C. 102 would not render obvious another compound of the same claim under 35 U.S.C. 103..

This application has been found to contain more than one patentably distinct inventions.

Therefore, the restriction/election requirement is still deemed proper and is therefore maintained further.

First action on merits follows.

Information Disclosure Statement

2. The IDS papers filed as paper # 7 dated 2/10/03 has been reviewed by the examiner, and a signed copy of the PTO Form 1449 is enclosed with this communication for applicants' record.

Claim Objections

3. Claims 10 ,15 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 9. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3,9,11-14,16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply.

(A). Claim 1 and 2 recite R1 as: " –OPO3 C1-4alkyl". The valence of P is not properly satisfied. Correction is required.

(B). Claim 1 on page 168, lines 23-24 define R33 and R34 as : ".. they are attached to forms a 4 to 14 atom ring...". Correction is required.

(C). Claim 1 recites component A as: " a saturated, unsaturated, or a partially unsaturated bicyclic heterocyclic ring structure substituted with R6, R7, R8, R9, and R20". The claim does not represent exactly and definitely the positions occupied on to the specific carbon atoms of bicycle(s). This definition will create confusion for the numbering of positions of the variables.

(D). In claim 1 when B = Aryl/Phenyl ; R2,R3,R4 = H, the claim can not differentiate the structures when R5 = H (or OH or Halogen etc., and when R1 = Halogen(or H or OH or other groups).

(E). Independent claim 2 recites A component as having X, Y, Z groups, but the same are not defined. Correction is required.

(F). Claim 11 recites : " ... comprising administering t a patient...". Correction is required.

(G). The" provisos" in claims 1, 2 are not very clear. If these provisos are to exclude the prior art(s) applicants are urged to provide the same with their relevancies to the instant application for further consideration.

(H). The method of use claims 12 and 16 recite the compounds of claim 2 which is an independent claim. Method of use for compounds and compositions of claim 1 is not recited. Therefore, it is very confusing to read exactly what applicants want to present in the claims. Correction is required.

Claim Rej ctions - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3,9,12-14 related to compounds and composition, and claims 11,16 related to method of use are rejected under 35 U.S.C. 102(b) as being anticipated by Iwanowicz et al (Biorg. & Med. Chem. Letr. 6/12, 1339-44(1996). The ref. Iwanowicz teaches making of compounds in scheme 1 on page 1340 and also in Table 1 compounds 1,13-22.

The instant claims encompasses these compound when the variables have following meanings:

A = indole; B= phenyl, and the variables:
R1 = OH, halogen, alkyl, S-alkyl;
R2-R5 = H,, Halogen,CN, alkyl,SH, OR10;
R6/R8/R9 = H,Halogen,CN,alkyl,NO2, O-Aryl,O-alkyl;
R7 =-C(=NH)-NH2, CONH2, C(=NH0-NH-NH2;
R20 = R24 = R10 as recited in page 168 lines 3-11, and in page 167, lines 21-25.

Claims 1-3,9,12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Kanda, Nobuo et al (EP 273418, also cited as Chemical Abstract DN 110:85613).

The compound having CAS RN# 118234-55-2(= Phenol, 2-(5-methyl- 1H-indol-2-yl) reads on the instant claims with the variables as defined earlier as:

A = indole; B= phenyl, and the variables:
R1 = OH, halogen, alkyl, S-alkyl;
R2-R5 = H,, Halogen,CN, alkyl,SH, OR10;
R6/R8/R9 = H,Halogen,CN,alkyl,NO2, O-Aryl,O-alkyl;
R7 =-C(=NH)-NH2, CONH2, C(=NH0-NH-NH2;

R20 = R24 = R10 as recited in page 168 lines 3-11, and in page 167, lines 21-25

Claims1-3,9,12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by McKinnon et al (Canadian J. Chem., 66/6, 1405-9(1988), also cited as Chemical Abstract DN 109:190304).

Following compounds read on the instant claims with variables as defined earlier as:

A = indole; B= phenyl, and the variables:
R1 = OH, halogen, alkyl, S-alkyl;
R2-R5 = H,, Halogen,CN, alkyl,SH, OR10;
R6/R8/R9 = H,Halogen,CN,alkyl,NO2, O-Aryl,O-alkyl;
R7 =-C(=NH)-NH2, CONH2, C(=NH0-NH-NH2;
R20 = R24 = R10 as recited in page 168 lines 3-11, and in page 167, lines 21-25

CAS RN # 117136-97-7(= Benzenethiol, 4-methyl-2-(3-methyl-1H-indol-2-yl);

CAS RN # 117136-95-5(=Benzenethiol,2-(1H-indol-3-yl) ;

CAS RN # 117136-96-6(=Benzenethiol, 2-(1H-indol-2-yl)-4-methyl-;

CAS RN # 117136-92-2P(=I1H-Indole,2-[2-(methylthio)phenyl]-;

CAS RN # 117136-94-4(=.1H-Indole,3-methyl-2-[5-methyl-2-(methylthio)phenyl];

CAS RN # 117136-93-3(=.1H-Indole,2-[5-methyl-2-(methylthio)phenyl].

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11,16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating arterial thromboembolism, does not

reasonably provide enablement for prevention of thromboembolic disorders, and prevention of cancer by the instant compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The claims refer to combined pharmacological activity as inhibitors of urokinase-type plasminogen activator(uPA) as well as inhibitors of Factor Xa. These inhibitors are related to many diseases, and diseases yet to be discovered, as outlined in the claims.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: **(1).** *The nature of invention;* **(2).** *the state of prior art ;* **(3).** *the predictability or lack thereof in the art;* **(4).** *the amount of direction or guidance present;* **(5).** *the presence or absence of working examples;* **(6).** *the breadth of the claims, and* **(7).** *the quantity of experimentation needed.*

Discussion about cancer(s):

For example, the claims set forth not only the treatment of a specific cancer, but also prevention of cancers and other diseases, generally. However, there never has been a compound capable of treating various types of cancers. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancers and pain as recited earlier, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologist today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. This is only for one of the many disorders as claimed herein.

Following references are quoted to show the state of art:

Cecil Textbook of Medicine states that: " each specific type of cancer has unique biological and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see In re Butting, 163, USPQ 689 (CCPA

1969), wherein "evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers".

Structure-Based Design of Novel Anticancer Agent:

Uckun et al(see Current Cancer Drug Targets, 1,59-71(2001) concludes in pages 66-67 that : " WHI-P131, which inhibits JAK3 but does not inhibit JAK1, JAK2, SYK,BTK,LYN or IRP even at concentrations as high as 350uM is undergoing further studies to evaluate its potential use as a new anti leukemic agent(in children).

Agents that inhibit epidermal growth factor receptor(EGFR) may be useful for treatment of breast cancer.

Tubulin modulating agents, which are of natural as well as synthetic origin, can be used as effective anticancer agents for treating breast cancer.

COBRA compounds caused destruction of microtubule organization and apoptosis. Like other microtubule-interfering agents, COBRA compounds activated the proapoptotic c-Jun N-terminal kinase (JNK) signal transduction pathway, as evidenced by rapid induction of c-jun expression".

- ***Controversy with regard to the thrombigenicity of atrial flutter in comparision with atrial fibrillation***:

Gronefeld et al(pubMed Abstract 12687838, also cited as Pacing Clin. Electrophysiol. 26/1,323-7(2003)) state that: " There is a significant risk for thromboembolism in patients referred for ablation of typical artrial flutter who have not been appropriately anticoagulated".

- ***Information data for thromboembolism in patients with heart failure:***

De Lorenzo et al(PunMed Abstract, also cited as Drugs, 63/6 565-76(2003)) state that: " At present, **there is a lack of randomized data,** and the incidence of bleeding complications in patients with heart failure has caused a **decrease in use of oral anticoagulants for the prevention of thrombosis".**

- ***Relationship of Urokinase plasmminogen activating system & Vascular endothelial growth factor:***

Kaneko et al (PubMed Abstract 12708473, also cited as Cancer Sci. 94/1,43-9(2003)) state that : " PA system and VEGF **contribute synergetically to tumor progression.** Furthermore, multivariate analysis demonstrated that depth of tumor invasion, lymph node involvement and uPA expression were independent prognostic factors. UPA is a key factor in PA system, being **associated with poor outcome of gastric cancer**, and contributing not only to invasive activity, but also to angeogenesis".

Specification on pages 155-157 recite methods of assay and test carried out for the present invention. Table IV on page157 recites the comparative values of uPA as KiuM and Fxa as Ki iM for selected 8 compounds.

- Note, there are no test/assay results for the elected species.
- The uPA values range from 0.004 to 2.50.
- The Fxa values range from 0.00618 to 5.4.

- There is no test/assay for art recognized ref. Compound for comparison.

These results are not sufficient to support the methods of use claims not claiming treating of a specific cancer but in addition to treating, prevention of various cancers, and other diseases. Therefore, these results will help as preliminary guideline for screening the compounds only, and for preventing all the diseases as recited in the claims.

Statements of utility, which relate to or imply to treatment of a disease are subject to closer scrutiny. Ex parte Moore et al.(POBA 1960) 128 USPQ 8. Claims 11,16 do not meet the Utility Guidelines. The claims do not qualify as one utility statement, and are not believable on their face. Claims will require too much experimentation to determine what patient dosage relationship would produce what results. It is not believable on its face that any one compound would have all of those utilities. In re Hozumi, 226 USPQ 353.

Evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of claims directed to a method of treating 7 types of cancer with member of a class of several compounds. In re Buting, (CCPA 1969) 418 F2d 540, 163 USPQ 689.

The instant claims relate not only to treatment of a specific cancer(s), but also to prevention of caner(s), but other diseases as recited herein.

The quantity of experimentation need would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skilled in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims involving use of compounds, their compositions.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is 703 308 4709. The examiner can normally be reached on 6:30 to 5:00 pm (Monday-Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on 703 308 4716 or Sr. Examiner Mr. Richard Raymond at (703) 308 4523.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.

JOHN M. FORD
PRIMARY EXAMINER
GROUP - ART UNIT 1624

SP/June 20, 2003.